

## **REMARKS**

Claims 1-4, 6-11, and 13-18 are pending. Claim 1-4, 6, 9-11, and 14-17 have been amended. Claim 18 has been amended herein. No new matter has been inserted. Support for the amendment to the claims that added "intact" target cells can be found at least at page 4, line 29. Support for the phrase " intact target cell or a population of the same type of intact target cells" in new claim 18 can be found at least at page 6, line 36- page 7, line 1. Favorable reconsideration is respectfully requested in light of the amendments and remarks submitted herein.

### **Rejections Under 35 U.S.C. §103(a)**

Claims 1-4, 6-11 and 13-17 remain rejected as being obvious over Hajek et al. (US 5,340,719) in view of Fodstad et al. (WO 94/07139) and O'Briant (Cancer 68(6):1272, 1991).

Applicant respectfully asserts that the Examiner has failed to establish a *prima facie* case of obviousness. In order to establish *prima facie* obviousness, three basic criteria must be met, namely: (1) there must be some suggestion or motivation to combine the references or modify the reference teaching; (2) there must be a reasonable expectation of success; and (3) the reference or references when combined must teach or suggest each claim limitation. Applicant submits that the Office Action failed to state a *prima facie* case of obviousness, and therefore the burden has not properly shifted to Applicant to present evidence of nonobviousness.

Applicant respectfully asserts that there would be no motivation to modify the teaching of the references because to do so would render Fodstad unusable for its intended purpose. With regard to Fodstad, the Examiner notes that "for increasing specificity, the second set of antibodies would be directed to a different type of cells".

The method of Applicant, on the other hand, begins with a suspension of single cells. A conjugate of particles is added to the suspension with specific antibodies adhered to the surface of the particles. There is only one type of antibody per particle. The particles however can be different colors or fluoresce at different wavelengths, and the different particles can have different antibodies adhered to their surface. However, all of the different antibodies are directed to antigens that are expressed on the surface of the target cells. Therefore, the suspension may contain four different particles, for example with four different antibodies, all directed to the same cell. Provided at exhibit A is an electronmicrograph of a cell particle conjugate that shows

different particles bound to the surface of a target cell. Each target cell of that particular type in the cell suspension may have several different particles bound to its surface, depending on the amount of antigens and to what degree the particle-antibody conjugate recognizes the different antigen. It is the numerous antibody-particle conjugates that bind to only one particular type of target cell that provide the high specificity of the Applicant's invention.

Therefore, if one of skill in the art modified Fodstad to use a second set of antibodies for the same type of cells, Fodstad would be rendered unusable for its intended purpose. Therefore, according to MPEP § 2143.01, there is no motivation to modify or combine the references to obtain Applicant's invention.

Furthermore, one of skill in the art would not have been motivated to modify the method of Hajek because the methodologies are too far afield. In the method of Hajek, and other methods that use dead cells, one is generally interested in the majority of the cells, as opposed to the aim of detecting a very small number of target cells of the same type, as Applicants do. In the case where the interest lies in the majority of the cells, as it does in Hajek, the cells are usually fixed before proceeding further, this is opposite to that of Applicant's invention. In the Applicant's invention, one of skill in the art would have to be lead to, and have the appropriate skills to detect a small number of cells, which required experimentation with the concentration of antibodies, the affinity of the antibodies, the amounts of particles, and conditions such as incubation time and temperature, etc.

Furthermore, there would be no reasonable expectation of success in modifying Hajek for example, because Hajek utilizes dead cells in their method. On the other hand, Applicant's method utilizes, and relies on intact, living cells. One of skill in the art knows that dead cells, as are used in the method of Hajek rupture in a suspension and could not be used in this type of method, because the antigens on the surface of the cells are destroyed, making it impossible to have optimal binding to the antibodies. The Applicant's method allows the cells to be collected, and used in further studies where it is necessary to have living cells.

The Applicant also respectfully wishes to point out some apparent inconsistencies in the Examiner's comments. On page 3, the Examiner initially indicates that Fodstad does "not preclude that the second set of antibodies could be directed to the same type of cells as the first antibody-particle complex". Then, she states "different from Applicant interpretation... one would recognize that for increasing specificity, the second set of antibodies would be directed to

a different type of cells as the first antibody-particle complexes, to distinguish different type of cells, thus increasing the specificity". These statements seem to contradict each other, and the Applicant asks the Examiner to reiterate her position with respect to this point.

Furthermore, the Examiner refers to the "plurality of antibodies" disclosed in Hajek, but then writes "Further, O'Briant... multiple monoclonal antibodies can compensate for the heterogeneity of antigenic phenotype within and between tumors." The Applicant's method does not attempt to compensate for anything at all, but instead detects the expression of several antigens on single cells, but does not detect several cells due to the heterogeneity within a tumor or between tumors.

The Examiner also notes, on page 4 of the action that Fodstad and Hajek, in combination, would have made a "person skilled in the art" "motivated to phenotype within and between tumors". This is however not what Applicant is hoping to accomplish, and is not what the claims are directed to.

Applicant respectfully requests that the Examiner reconsider the rejection of the pending claims in light of the claim amendments, new claim, and comments offered above.

### Conclusion

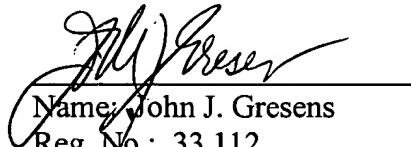
It is respectfully submitted that each of the presently pending claims is in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' representative at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted,

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